HPV-008: Phase III Study of the Efficacy of GSK's Cervical Cancer Candidate Vaccine in 15 to 25 Year Old Women

Planned Interim Analysis Results

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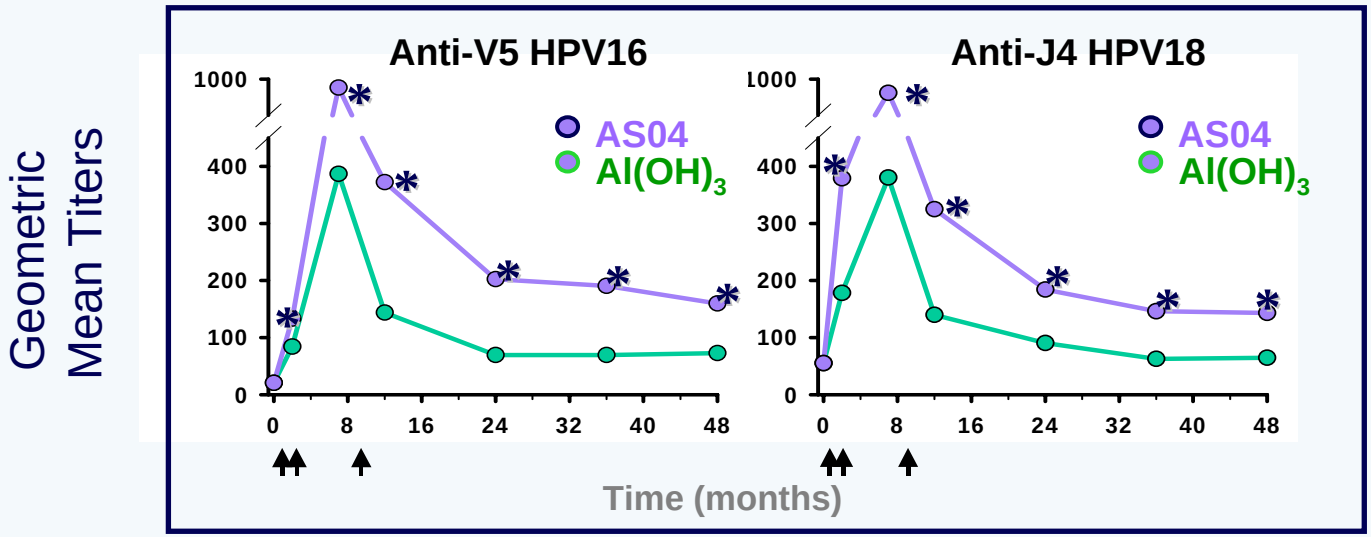
ACIP, June 28, 2007

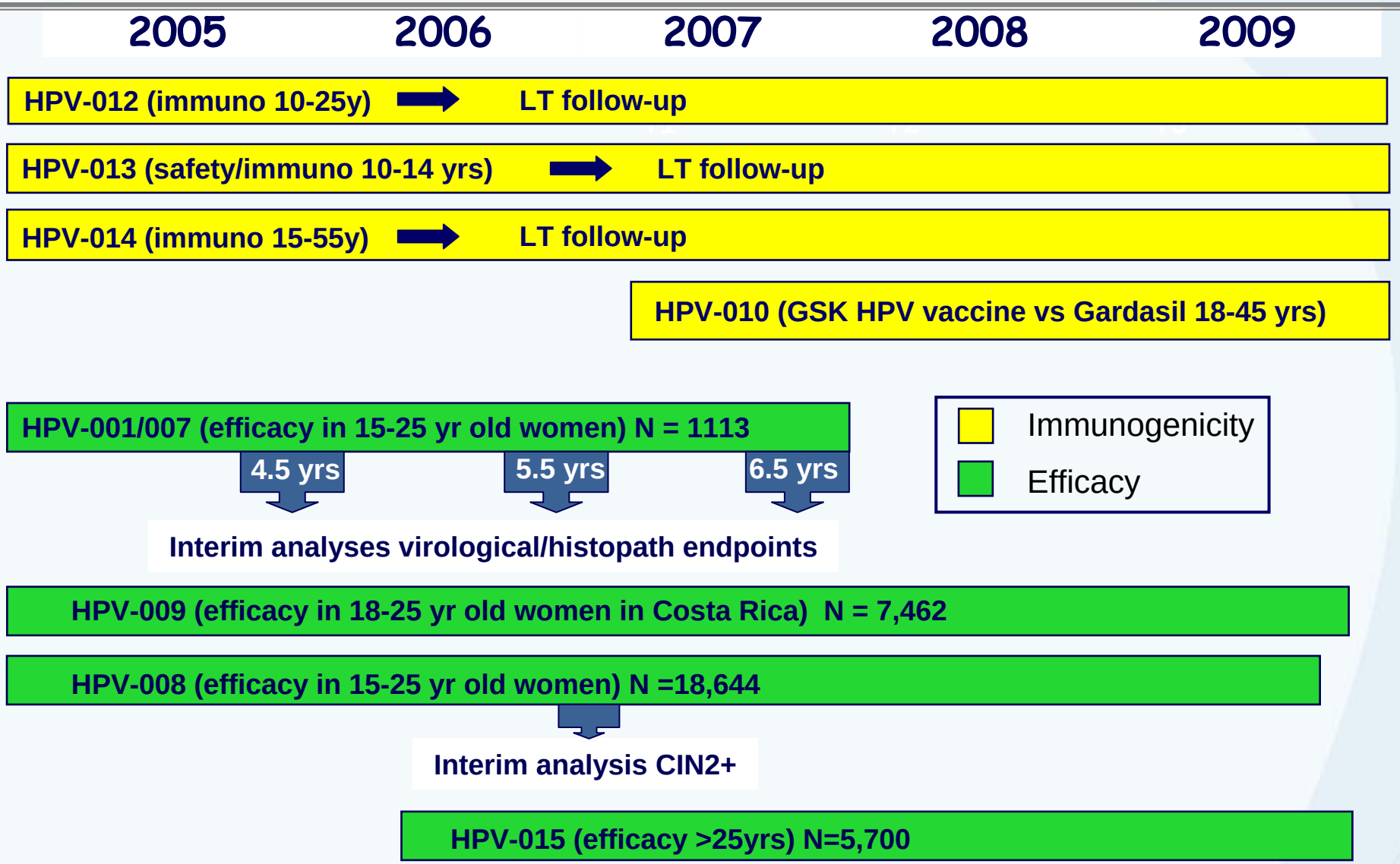
GSK Cervical Cancer Vaccine

- Vaccine formulation:
  - HPV-16/18 L1 virus-like particles (20μg each type)
  - AS04 adjuvant: 50μg MPL + 500μg aluminium hydroxide
- Rationale for formulation:
  - HPV-16/18 responsible for ~70% of cervical ca globally
  - AS04 adjuvant designed to enhance immunogenicity



- Studies conducted in women 10-55 years of age

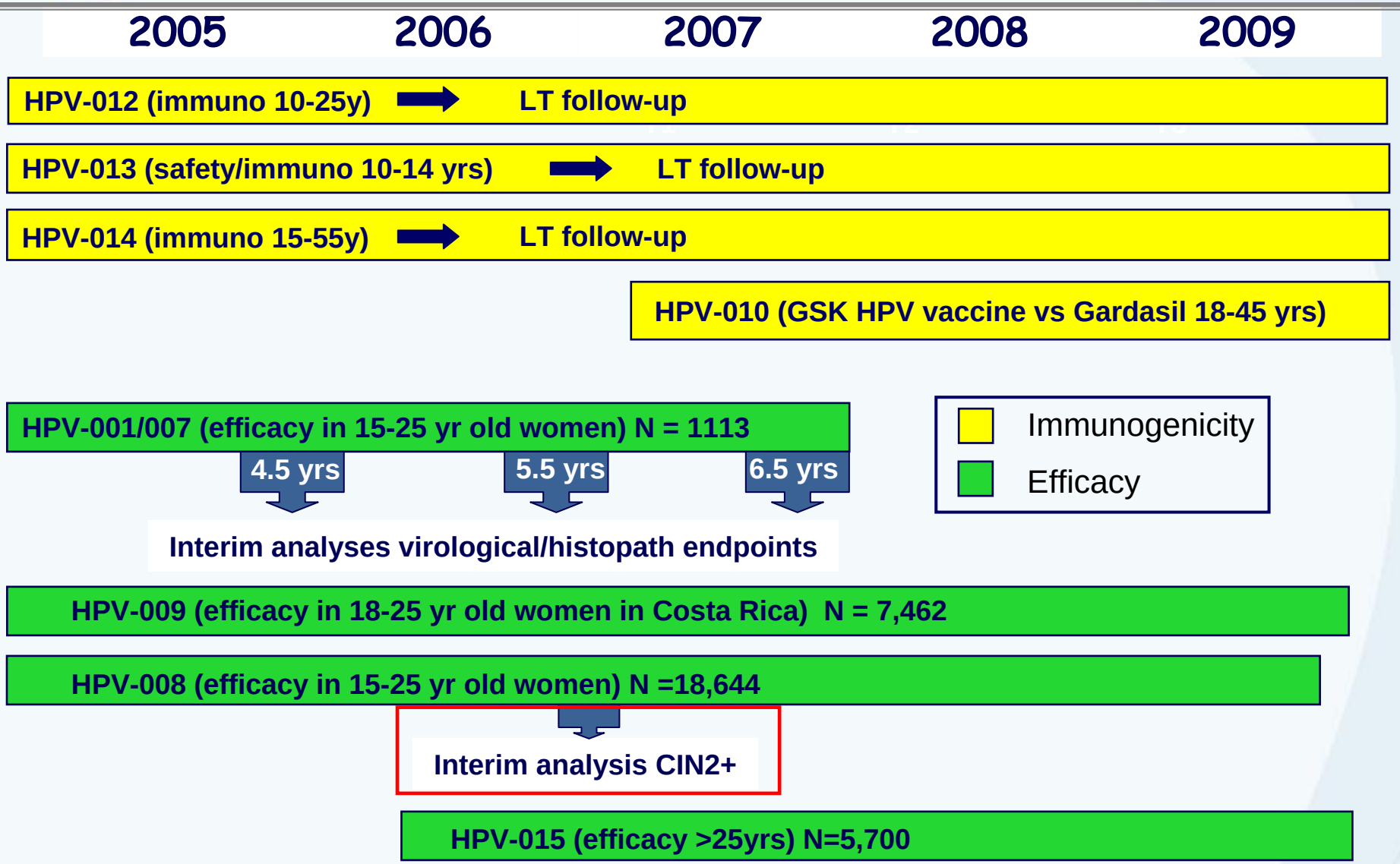
Summary of Ongoing Phase IIb/III Trials



Conclusions from Previous Studies

- GSK cervical cancer vaccine was generally well tolerated
- Vaccine efficacy of 100% in prevention of HPV16/18 endpoints, including persistent infection, abnormal cytology and CIN lesions in 15-25 year old women naïve to oncogenic HPV at study entry
- Cross protection against incident infection with HPV-45 and-31 which are, respectively
  - Phylogenetically related to HPV18 and 16
  - 3rd and 4th most common types associated with cervical cancer
- Immunobridging: well tolerated in 10-14 and 26-55 year old women with GMTs similar or greater than those associated with protection

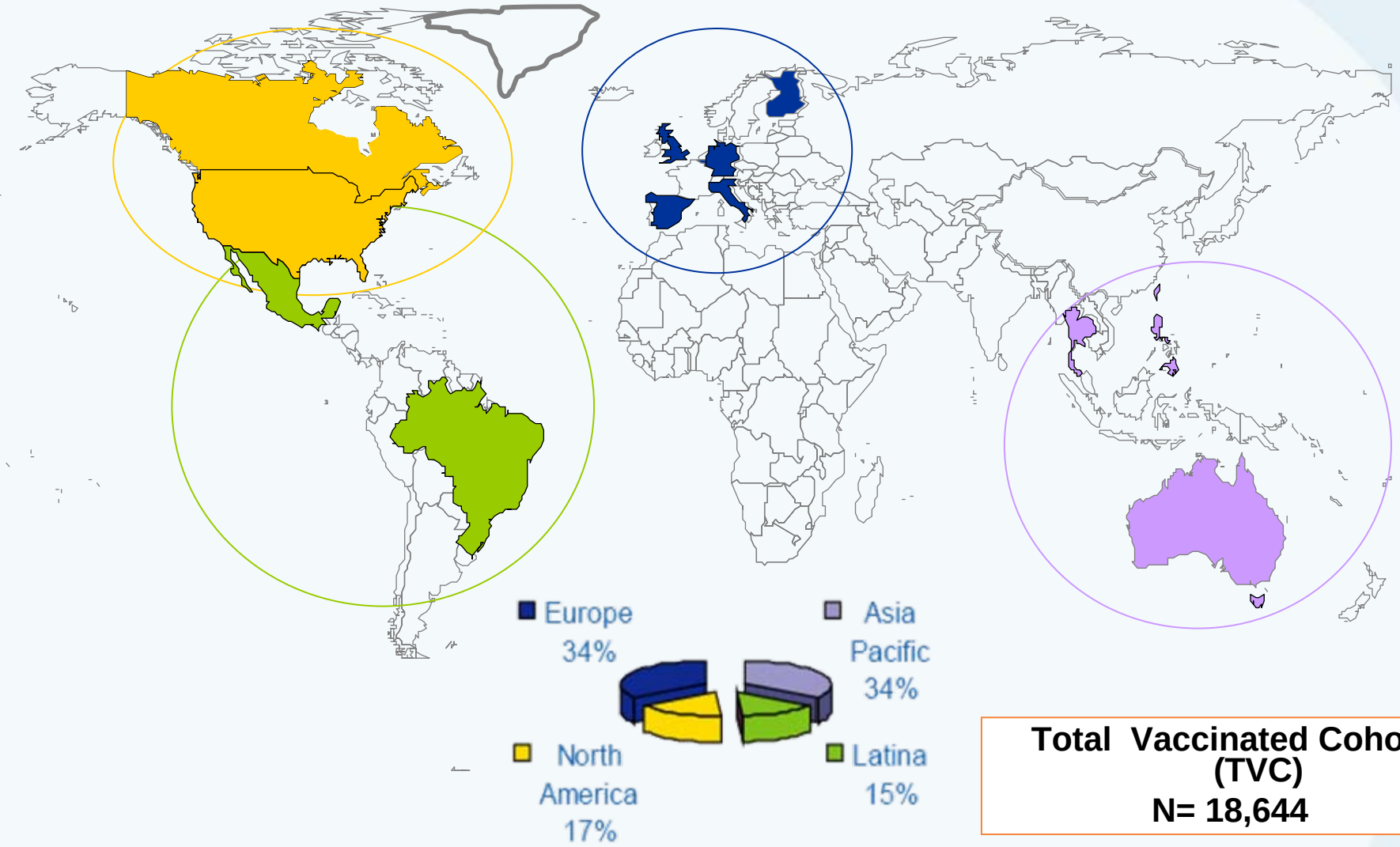
Summary of Ongoing Phase IIb/III Trials



HPV-008 Topics

- Study Population
- Study Design
- Results of planned pre-specified interim analysis
- Conclusions

HPV-008: Study Population



Total Vaccinated Cohort (TVC)
N= 18,644

HPV-008: Study Population

- Unscreened women 15-25 years old
  - Includes women with current or prior oncogenic HPV infection

Efficacy evaluation in a broad population

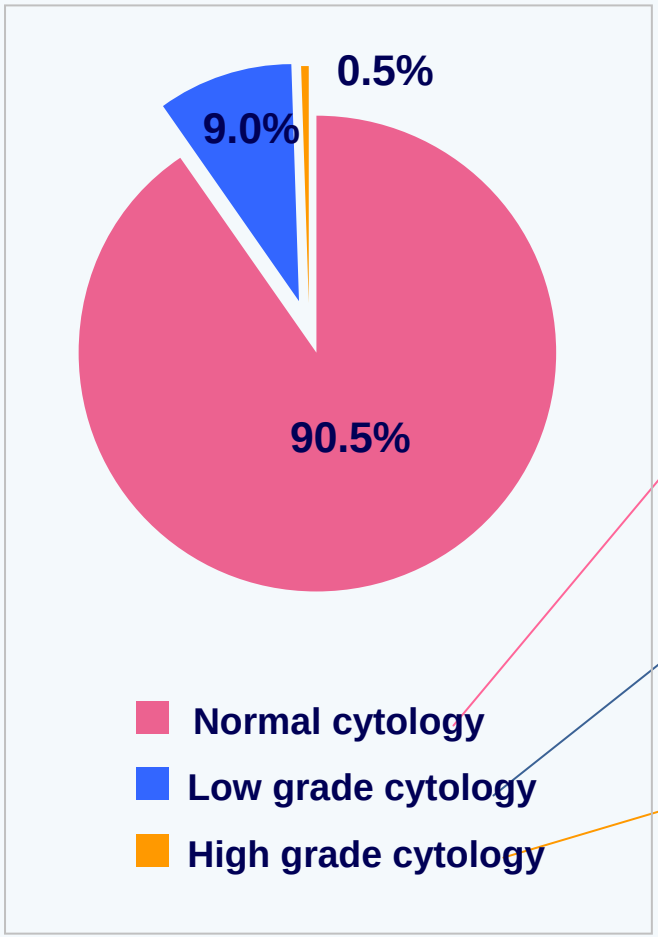
- At entry : Normal, low grade cytology and high grade cytology

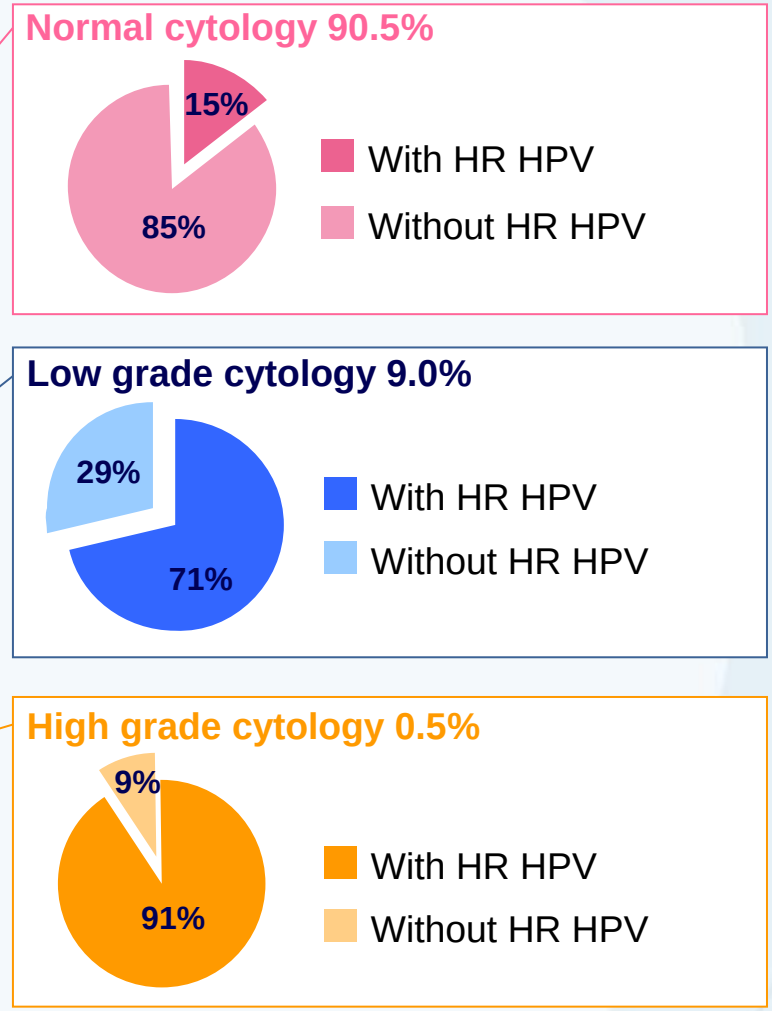
  Many women with oncogenic HPV infection

  High Grade cytology was excluded from interim analysis

- At least 1 vaccine dose
  - Case counting for efficacy evaluation starts **from first vaccine dose**

HPV-008: Baseline Characteristics





HPV-008: Study Design

N=18,644 women vaccinated (TVC), aged 15-25 years old

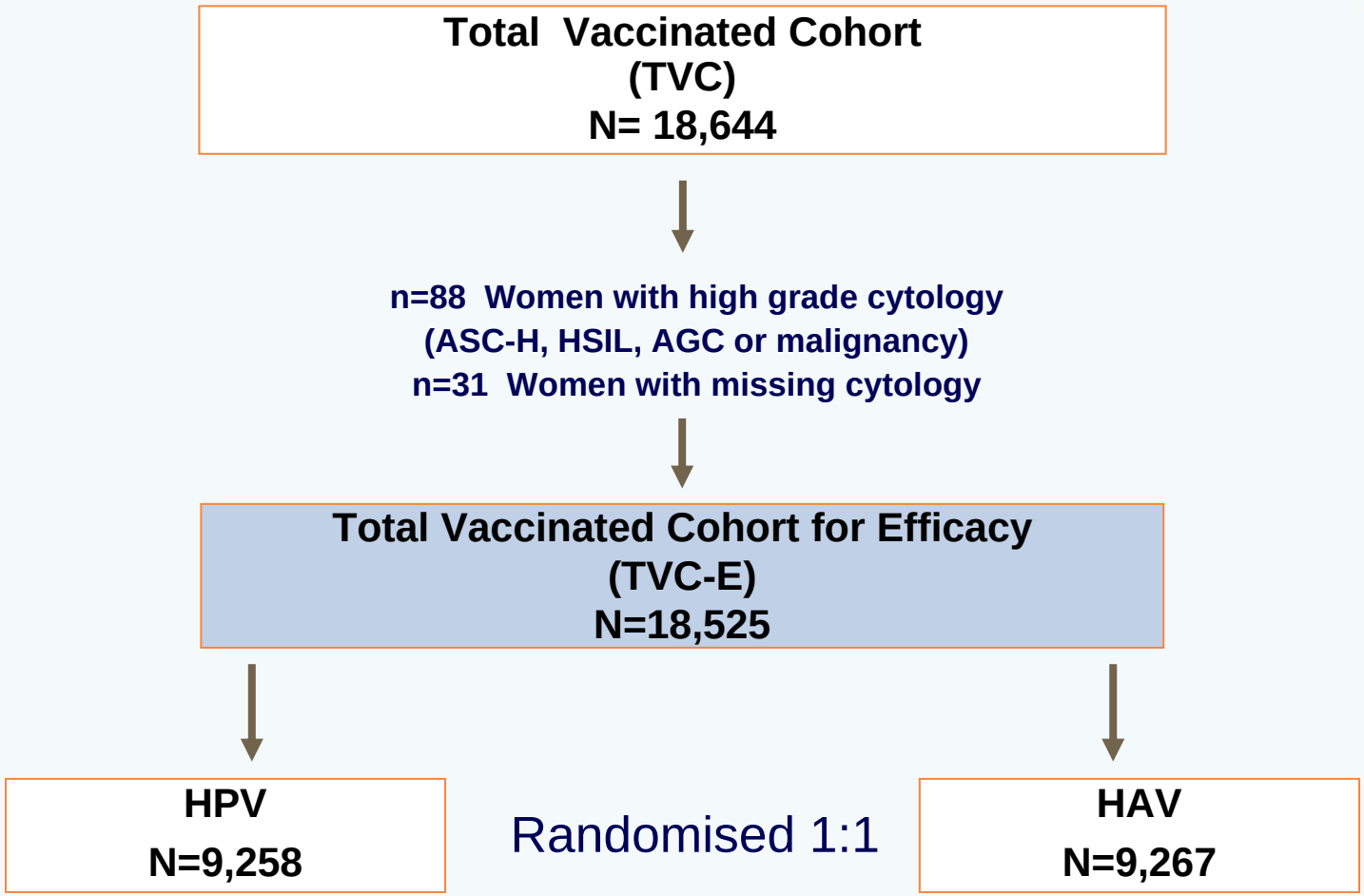
Randomized 1:1, Double Blind

Controlled (adapted formulation of GSK Hepatitis A vaccine)

Month	0	1	6	7	12	18	24	30	36	48
Visit	1	2	3	4	5	6	7	8	9	10
Serology	X		X	X	X		X		X	X
Cervical sample	X		X		X	X	X	X	X	X

Mean follow-up (15 Months)

HPV-008: Study Cohorts for Evaluation



HPV-008: Primary Efficacy Endpoint

- **To assess efficacy of the vaccine in the prevention of histopathologically-confirmed CIN2+ associated with HPV-16 or -18 in the cervical lesion**
  - CIN2+ lesion confirmed by consensus diagnosis using a panel of three independent histopathologists
  - Detection of HPV-16/18 DNA in the lesion by sensitive PCR algorithm:
    - 14 high-risk types detected by SPF10-LiPA: HPV-16, 18, 31, 33, 35, 39, 45, 51 52, 56, 58, 59, 66 and 68
    - Type specific HPV for HPV-16 and 18
  - Assessed in women who are HPV DNA negative and seronegative at study entry for the corresponding HPV type considered in the analysis
- **Use of broad spectrum PCR allows full characterization of lesions for vaccine and non-vaccine types**

HPV-008: Three Analyses are Planned

1. **Interim analysis**
   - Triggered when at least 23 cases of HPV-16/18 CIN2+ were available for total vaccinated cohort (TVC-E) analysis
2. Final analysis (event triggered)
3. Blinded extended follow-up of 4 years

HPV-008: Complexity of the Case Assessments

- HPV-008 is unique in that it provides full characterization of HPV natural history and multiple infections in CIN lesions:
  - High rate of prevalent HPV infections at study entry, mostly with normal cytology
  - 14 of the 23 CIN2+ lesions (61%) **showed more than one HPV type as detected by PCR**
  - 14 of the 23 lesions were derived from infections that were detected prior to completion of the 3 dose series

⇒ **This high rate of multiple infections in CIN lesions was not expected, based on published literature**

3 Patterns of HPV Detection in 23 CIN2+ Cases

Pattern 1: Single HPV type (HPV-16/18) in CIN2+ lesion preceded by infection with same type in cytology samples (9 cases)

	CERVICAL SAMPLES				Month 12 Triggered Management	
Case		**Month 0**	**Month 6**	**Month 12**	**Punch**	**LEEP**
17	HPV DNA	N	**HPV-18**	**HPV-18**	CIN2: **HPV-18** 27days after month 12	

3 Patterns of HPV Detection in 23 CIN2+ Cases

Pattern 2: Multiple HPV types in the CIN2+ lesion with 16 or 18 infection in preceding samples (11 cases)

	CERVICAL SAMPLES				Month 12 Triggered Management	
Case		**Month 0**	**Month 6**	**Month 12**	**Punch**	**LEEP**
13	HPV DNA	N	**HPV-16/51**/59	**HPV-16/51**/52	CIN2: **HPV-16/51** 29 days after month 12	CIN2 **HPV-16/51**/56/68 76 days after month 12

3 Patterns of HPV Detection in 23 CIN2+ Cases

Pattern 3: Multiple HPV types in the CIN2+ lesion with no infection for the type considered for efficacy (16 or 18) in preceding samples (3 cases)

What type is the cause of these lesions?

Pattern 3: Multiple HPV types in CIN2+ lesion with no infection with the type considered for efficacy (16 or 18) in preceding samples

	CERVICAL SAMPLES				Month 12 Triggered Management	
Case		**Month 0**	**Month 6**	**Month 12**	**Punch Biopsy**	**LEEP**
1	HPV DNA				CIN3: **HPV-16/58** 36days after month 12	CIN3: **HPV-58** 113days after month 12 Same lesion
2	HPV DNA					
22	HPV DNA					

Pattern 3: Multiple HPV types in CIN2+ lesion with no infection with the type considered for efficacy (16 or 18) in preceding samples

		CERVICAL SAMPLES			Month 12 Triggered Management	
Case		**Month 0**	**Month 6**	**Month 12**	**Punch Biopsy**	**LEEP**
1	HPV DNA	**HPV-58**	**HPV-58**	**HPV-58**	CIN3: **HPV-16/58** 36days after month 12	CIN3: **HPV-58** 113days after month 12 Same lesion
2	HPV DNA					
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2	HPV DNA				CIN2: **HPV-18/58** 35days after month 12	**Normal** 70days after month 12
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22	HPV DNA				CIN3: **HPV-16** At month 12	**Cone biopsy** 42 days after month12 visit **1 CIN1 HPV-16** **7 CIN3 HPV-16** **1 CIN3 HPV-16 / 18**

Pattern 3: Multiple HPV types in CIN2+ lesion with no infection with the type considered for efficacy (16 or 18) in preceding samples

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22	HPV DNA	**16/51/52 /54**	**16/51/52**	**HPV -16**	CIN3: **HPV-16** At month 12	**Cone biopsy** 42 days after month12 visit **1 CIN1 HPV-16** **7 CIN3 HPV-16** **1 CIN3 HPV-16 / 18**

Pattern 3: Multiple HPV types in CIN2+ lesion with no infection with the type considered for efficacy (16 or 18) in preceding samples

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22	HPV DNA	**16/51/52 /54**	**16/51/52**	**HPV -16**	CIN3: **HPV-16** At month 12	**Cone biopsy** 42 days after month12 visit **1 CIN1 HPV-16** **7 CIN3 HPV-16** **1 CIN3 HPV-16 / 18**

Additional Efficacy Analysis

- **HPV type assignment algorithm**
  - If *more than one HPV type* is found in a lesion, presence of HPV in the 2 immediately preceding cytology samples evaluated
    - Causal association based on detection of HPV type in at least 1 preceding cytology sample*
  - Algorithm is based on the well established association between persistent oncogenic infections and development of CIN2+ lesions [1, 2]

[1] Wallin et al, NEJM 1999; 34:1633-8
[2] Ho et al, J Natl Cancer Inst 1995: 87:1365-71

*If none of the HPV types present in the lesion found in either of the 2 cytology samples, HPV types present in the lesion are considered associated with lesion

Efficacy against HPV-16/18 CIN2+ (TVC-E)

Pre-specified Case Definition based on PCR detection in lesion only

Endpoint	Group	N	n	Vaccine Efficacy(97.9% CI)			
				%	LL	UL	P-value
CIN2+ HPV-16/18	**HPV**	**7788**	**2**	**90.4**	**53.4**	**99.3**	**<0.0001**
	Control	**7838**	**21**				
CIN2+ HPV-16	HPV	6701	1	93.3	47.0	99.9	0.0005
	Control	6717	15				
CIN2+ HPV-18	HPV	7221	1	83.3	-78.8	99.9	0.1249
	Control	7258	6				

Analysis considering patterns of HPV types in preceding infection*

Endpoint	Group	N	n	Vaccine Efficacy (97.9% CI)			
				%	LL	UL	P-value
CIN2+ HPV-16/18	**HPV**	**7788**	**0**	**100**	**74.2**	**100**	**<0.0001**
	Control	**7838**	**20**				
CIN2+ HPV-16	HPV	6701	0	100	64.5	100	<0.0001
	Control	6717	15				
CIN2+ HPV-18	HPV	7221	0	100	-49.5	100	0.0625
	Control	7258	5				

***Post hoc**

Efficacy against HPV-16/18 CIN2+ Regardless of Serostatus (TVC-E)

Pre-specified Case Definition based on PCR detection in lesion only

Endpoint	Group	N	n	Vaccine Efficacy (97.9% CI)			
				%	LL	UL	P-value
CIN2+ HPV-16/18	**HPV**	**8293**	**2**	**91.6**	**60.2**	**99.4**	**<0.0001**
	Control	**8319**	**24**				
CIN2+ HPV-16	HPV	7884	1	**94.4**	56.8	99.9	<0.0001
	Control	7954	18				
CIN2+ HPV-18	HPV	8141	1	**83.2**	-78.9	99.9	0.1249
	Control	8173	6				

Analysis considering patterns of HPV types in preceding infection*

Endpoint	Group	N	n	Vaccine Efficacy (97.9% CI)			
				%	LL	UL	P-value
CIN2+ HPV-16/18	**HPV**	**8293**	**0**	**100**	**78.0**	**100**	**<0.0001**
	Control	**8319**	**23**				
CIN2+ HPV-16	HPV	7884	0	100	70.9	100	<0.0001
	Control	7954	18				
CIN2+ HPV-18	HPV	8141	0	100	-49.6	100	0.0625
	Control	8173	5				

***Post hoc**

HPV-008: Efficacy beyond HPV 16/18 (persistent infection)

Use of Persistent Infection Endpoints to Assess Protection against Other Types

- Persistent oncogenic HPV infection established as a necessary precursor for development of cervical cancer
- HPV PCR allows highly sensitive and reproducible detection of HPV in cervical samples
- Cervical lesions caused by less frequent HPV types (e.g., 45 and 31) may be associated with detection of multiple HPV types in the lesion
  - Causal association of type with lesion may be confounded
  - Use of persistent infection endpoint avoids possible confounding

HPV-008: Impact of Limited F/U time on Efficacy Against Persistent Infection

15 Months follow up at Interim Analysis

➔ ~90% of 12-month infections and ~ 70% of 6-month infections were acquired prior to Dose 3 of vaccine or control

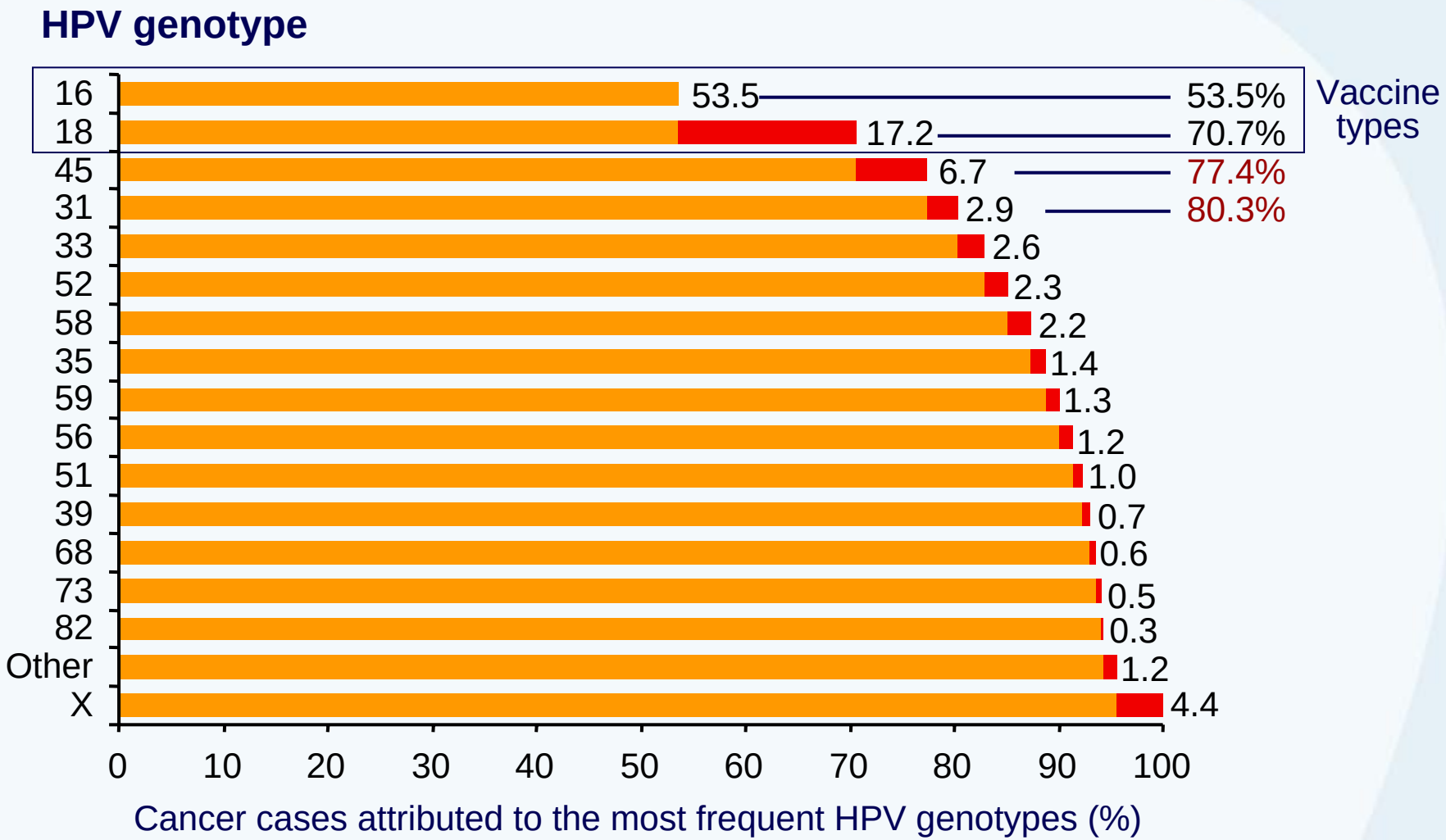
Efficacy Against Oncogenic HPV-types Beyond 16/18

6 Month Persistent Infection

	TVC-E (at least 1 dose)			
Type	**Vaccine (cases)**	**Control (cases)**	**Vaccine Efficacy**	**97.9% CI**
HPV-45	10	25	**59.9%**	2.6, 85.2
HPV-31	47	74	**36.1%**	0.5, 59.5

In ~70 % of these cases the onset of infection was before completion of the vaccination course.

HPV Types in Cervical Cancer Worldwide



Munoz N et al. Int J Cancer 2004; 111: 278–85.

Efficacy Against Oncogenic HPV-types Beyond 16/18

6 Month Persistent Infection

HPV type	Vaccine Efficacy (TVC-E) 97.9% CI			
	%	LL	UL	P-value
HPV-45	**59.9**	**2.6**	**85.2**	**0.0165**
HPV-31	**36.1**	**0.5**	**59.5**	**0.0173**
HPV-33	36.5	-9.9	64.0	0.0560
HPV-52	**31.6**	**3.5**	**51.9**	**0.0093**
HPV-58	-31.4	-132.1	24.7	0.2515
HPV-35	-10.2	-133.4	47.6	0.7650
HPV-59	-0.7	-105.3	50.6	1.0000
HPV-56	8.9	-40.6	41.2	0.6496
HPV-39	0.7	-49.6	34.1	1.0000
HPV-51	3.1	-33.2	29.5	0.8399
HPV-68	11.9	-40.9	45.2	0.5570
HPV-66	-38.2	-122.8	13.4	0.0997

In ~70 % of these cases the onset of infection was before completion of the vaccination course

Efficacy Against Oncogenic HPV-types Beyond 16/18

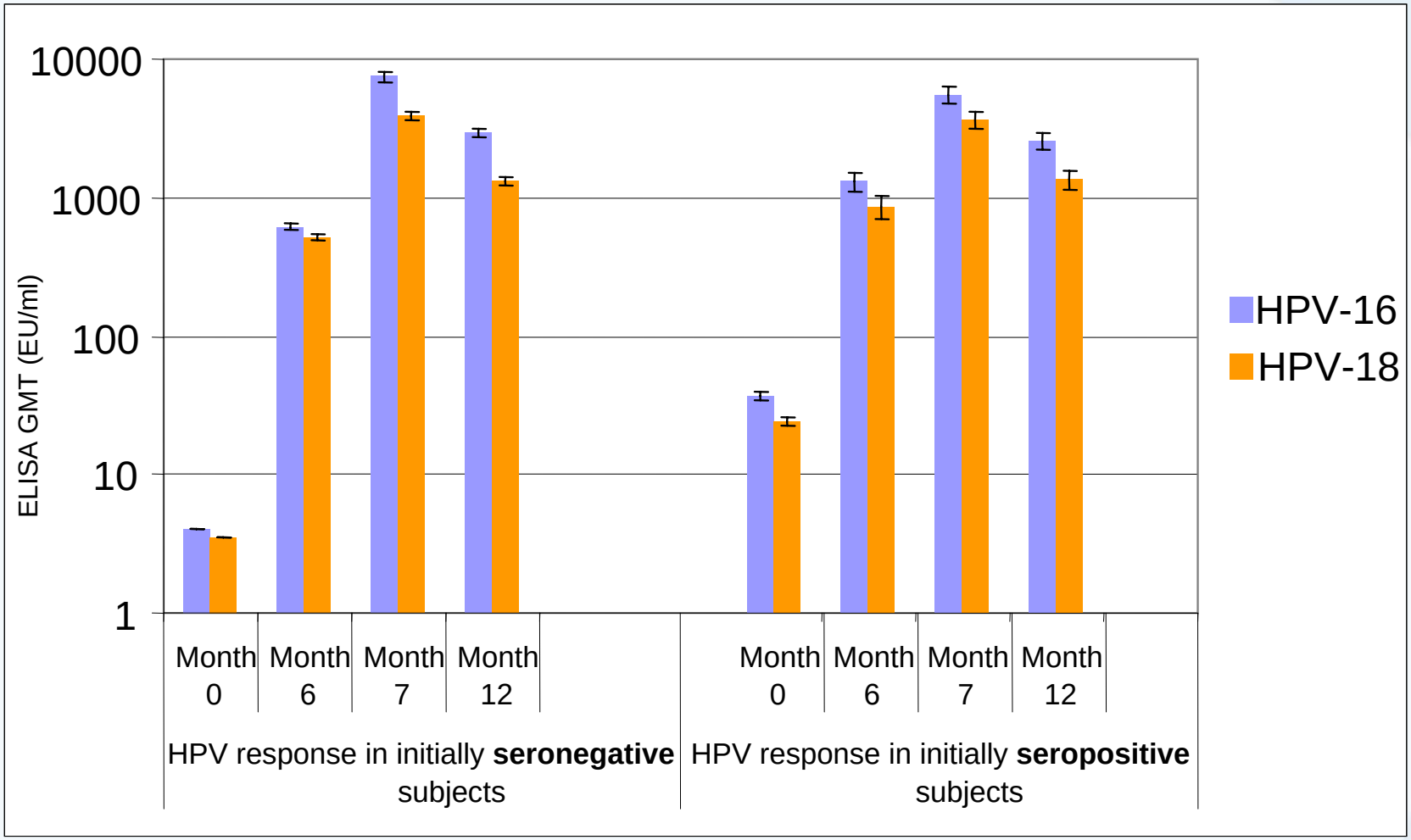
12 Month Persistent Infection

	TVC-E (at least 1 dose)			
HPV-type endpoint	**Vaccine (cases)**	**Control (cases)**	**Vaccine Efficacy**	**97.9% CI**
Oncogenic HPV types beyond 16 & 18	100	137	**27.1%**	0.5, 46.8

In ~90 % of these cases the onset of infection was before completion of the vaccination course

Immunogenicity

HPV-008: Immunogenicity (ATP cohort, ELISA)



HPV-16/18 seropositivity at time of vaccination does not negatively impact vaccine response

HPV-008: Safety Profile

HPV-008: Study Drop-outs

Characteristics	Parameters or Categories	HPV N = 9319		HAV N = 9325	
		n	%	n	%
Drop out	Yes	496	5.3	458	4.9
	No (study ongoing)	8823	94.7	8867	95.1
Reason for dropout	Serious Adverse Event	3	0.6	5	1.1
	Non-serious adverse event	6	1.2	3	0.7
	Protocol violation	5	1.0	6	1.3
	Consent withdrawal not due to AE	136	27.4	143	31.2
	Migrated/moved from study area	64	12.9	49	10.7
	Lost to follow-up	231	46.6	215	46.9
	Other	51	10.3	37	8.1

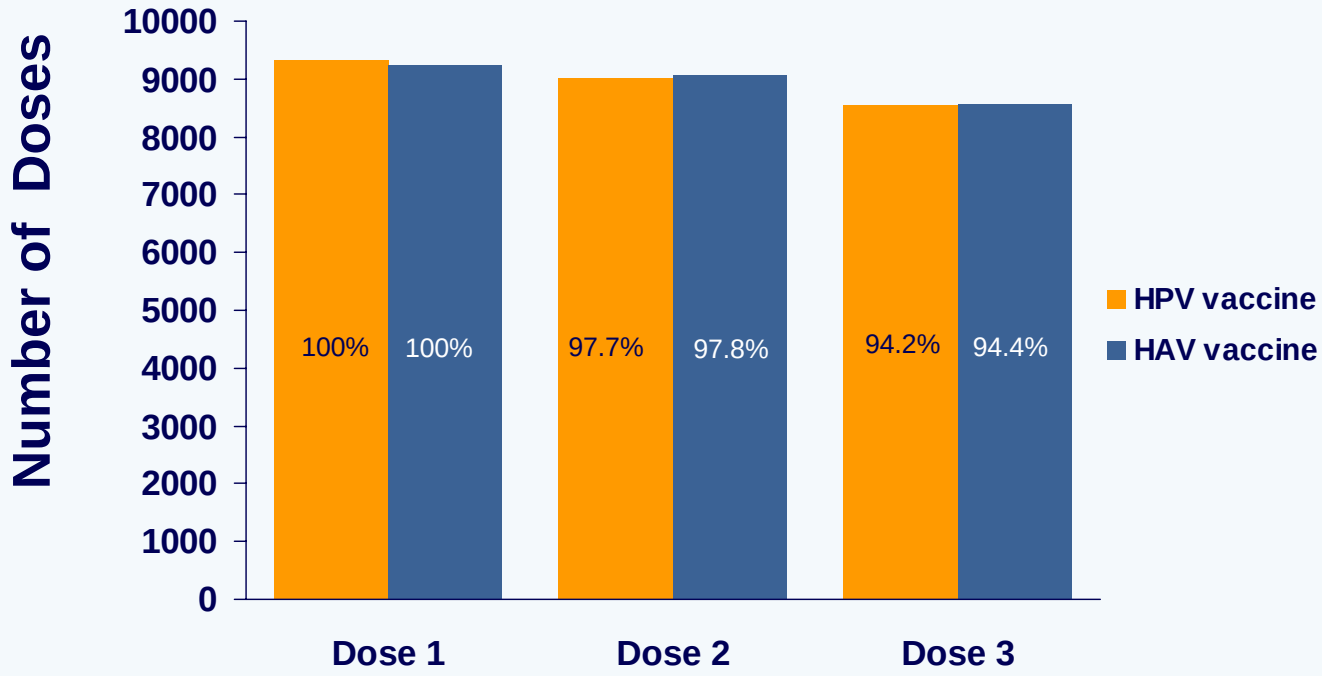
HPV-008: Overall Safety Profile

- Overall incidence of AEs reported during the 30-day period after each dose in diary card subset (includes solicited local and general symptoms for 7 days)

		Any symptom			General symptoms			Local symptoms		
	Group	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Overall number of women reporting a symptom	**HPV**	3077	2913	**94.7**	3076	2614	**85.0**	3077	2807	**91.2**
	HAV	3080	2773	**90.0**	3080	2514	**81.6**	3080	2460	**79.9**

- Local reactogenicity (pain, redness and swelling): higher in HPV group
- General symptoms: Slightly higher in HPV group
- No increase in local or general symptoms with subsequent doses

HPV-008: Compliance with Dosing



Similar compliance in both study groups

HPV-008: Solicited and Unsolicited AEs: Stratified by Baseline Sero/DNA status*

Cohort	Any symptom			General symptoms			Local symptoms		
	%	LL	UL	%	LL	UL	%	LL	UL
Total Vaccinated cohort	**85.4**	84.6	86.1	**65.8**	64.8	66.8	**81.3**	80.5	82.1
Sero - and DNA -	**85.8**	84.9	86.7	**66.7**	65.5	67.9	**82.0**	81.0	82.9
Sero + or DNA +	**84.3**	82.8	85.8	**63.7**	61.7	65.7	**79.8**	78.1	81.4
DNA +	**88.1**	85.3	90.4	**67.4**	63.7	71.0	**84.2**	81.2	86.9

Reactogenicity profile similar in all groups

*Overall incidence during the 30-day period after each dose

HPV-008: Safety Profile (TVC)

Safety Outcomes	HPV (N = 9319)	HAV (N = 9325)
Unsolicited Adverse Events: % of women with at least 1 event (95% CI)		
All unsolicited symptoms* (Day 0-29)	42.5% (60.8-44.3)	43.6% (41.9-45.3)
Medically significant conditions	21.3% (20.5-22.2)	21.8% (20.9-22.6)
New onset chronic diseases	1.5% (1.3-1.8)	1.7% (1.4-1.9)
New onset autoimmune diseases	0.3% (0.2-0.5)	0.3% (0.2-0.4)
Serious Adverse Events: number (%)		
Number of women reporting	330 (3.5%)	323 (3.5%)
Number of SAEs reported	389 (4.2%)	372 (4.0%)

*Diary card subset (3184 HPV recipients and 3187 HAV recipients)

HPV-008: Pregnancy and Safety

Pregnancies/ Pregnancy outcomes*	HPV (N = 9319)	HAV (N = 9325)
Number of pregnancies	665	685
Pregnancy ongoing	201 (30.2%)	233 (34%)
Normal infant	270 (40.6%)	264 (38.5%)
Abnormal infant	4 (0.6%)	8 (1.2%)
Premature births	15 (2.3%)	17 (2.5%)
Spontaneous abortion	66 (9.9%)	51 (7.4%)
Elective termination	87 (13.1%)	93 (13.6%)
Lost to follow-up	10 (1.5%)	13 (1.9%)

*Totals do not include blinded outcomes, ectopic pregnancies

HPV-008 Interim Analysis: Conclusions

- Largest HPV vaccine trial conducted to date
- First cervical cancer vaccine efficacy trial which provides full characterization of HPV natural history and multiple infections in CIN lesions
- High level protection against HPV-16/18 CIN2+ confirmed in a broad population of women (TVC-E)
  - VE = 90% against any CIN2+ lesions with HPV-16/18 detected in lesion only
  - VE = 100% against CIN2+ lesions where HPV-16/18 likely to be causally associated with lesion
  - High VE regardless of initial HPV16/18 serostatus
- Majority of endpoints (CIN2+ and persistent infections) derived from infections detected prior to completion of 3-dose series
  - Suggests early onset of vaccine effect

HPV-008 Interim Analysis: Conclusions

- HPV-008 extends previous evidence of cross-protection
  - Efficacy against HPV-45, 31, 52 using 6 month persistent infection
  - Efficacy against 12 month persistent infection in analysis of a combination of 12 non-vaccine oncogenic HPV types
  - Persistent infection as endpoint is not confounded by multiple types in biopsy
- HPV-16/18 L1 VLP AS04 vaccine was highly immunogenic and generally well tolerated

Back ups

Additional Assessment

	Case	Biopsy Result	HPV DNA on cervical samples			E4 Immunostaining	
			M0	M6	M12	16/31	18
Cases	1	CIN3 Punch 36 days after M12 (16/58)	58	58	58	negative	negative
	2	CIN2 Punch 35 days after M12 (18/58)	58	Negative	58	negative	negative
	22	CIN3 Cone 42 days after M12 (16/18)	16,51,52,54	16,51,52	16	positive	negative
Control	13	CIN3 LEEP 76 days after M12 (16/51/56/58)	Negative	16,51,59	16,51,52	positive	negative
	17	CIN2 Punch 27 days after M12 (18)	Negative	18	18	negative	positive

- HPV-16/18 E4 staining performed on the 3 CIN2+ lesions not believed to be causally associated with detected types
- Absence of E4 expression in these lesions confirmed

Advisory Committee on Immunization Practices

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